THE IMMUNIZING EFFECTS OF ANTITOXIN

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THE IMMUNIZING EFFECTS OF ANTITOXIN.[1]

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BEFORE describing the results obtained from 438 immunizing injections of antitoxin at the Children's Hospital, I will briefly explain the reasons which have rendered such an extensive use of the serum necessary.

The policy of the institution has always been to decline to admit cases of such diseases as are generally regarded as infectious; and the building originally included but two small rooms for the isolation of such cases as might appear among the patients in the house. After a time (as might be naturally expected in any large congregation of children), endemics occurred, and larger, but (in the light of recently acquired experience) insufficient quarters were provided.

During the year 1894, cases of diphtheria occurred so frequently as to necessitate the closing of the hospital, and disinfection of the wards, on three separate occasions; to the great inconvenience of all concerned, and with serious detriment to the usefulness of the institution.

It was thought at first, that the infection was introduced by the parents or friends of the patients; and blouses and disinfectant washes for the faces and hands of all visitors were prescribed. But in spite of these precautions, fresh outbreaks occurred, and we were reluctantly forced to the conclusion that the Klebs-Löffler bacillus had installed itself as a perma-

[1] Read before the American Pediatric Society, Hot Springs of Virginia, May 27, 1895.

nent and most unwelcome guest within our walls, and stood in no need of an introduction.

Furthermore we convinced ourselves that the chief source of trouble was confined to one ward, where grave defects of ventilation were discovered. Some time elapsed before this last conclusion was reached; for while cases of diphtheria were more frequent in this ward than elsewhere, the fact that the majority of the children were in the habit of meeting in the playroom, had led to such a distribution of the infection as to give rise to cases in all parts of the hospital. The type which the disease assumed was seldom frank; children with coryza or slight tonsillitis and scarcely any constitutional symptoms, would perhaps fatally infect others, and in many instances repeated bacteriological examinations of the secretions alone showed when the trouble began and ended — no membrane or other clinical evidence of diphtheria being present at any time.

January 13, 1895, there were nine cases in the infectious wards, four or five of which had been transferred from the house within forty-eight hours.

The question of closing the hospital for the fourth time was discussed, and it was decided to first try immunization with antitoxin, in the hope that this course might enable us to maintain open doors and go on with our work. The staff was so kind as to give me *carte blanche*, so far as the diphtheria was concerned, and within thirty-six hours, thirty-nine patients who remained in the house, and three nurses who were on duty in the contagious wards, received each an injection of five cubic centimetres of the serum prepared at the Pasteur Institute of New York, according to the formula of Roux.

The apparent result of this first attempt was to instantly arrest any further spread of the disease. Pa-

tients in the contagious wards were disinfected and returned to the house as soon as negative reports of the cultures of two specimens taken forty-eight hours apart, were received from the bacteriological laboratory of the Harvard Medical School. No patients were admitted with any suspicious symptoms in their noses or throats; and all new-comers received an injection of five cubic centimetres on entrance. Specimens were obtained frequently from all patients, and reports of the cultures were all negative until January 29th, when a boy who had reacted perfectly well to an immunizing dose, was found guilty of harboring the Klebs-Löffler bacillus, and was at once transferred to the contagious wards. The specimen from which this positive culture was obtained, was taken sixteen days after immunization; and while there was no certainty that the bacillus had not been present for an indefinite time in this particular case (through an oversight, no previous culture having been made) it was thought best to inject antitoxin again in all cases which had not been immunized within ten days. Cultures were now made at the bacteriological laboratory of the Harvard Medical School, of specimens from every nose and throat in the house, and negative reports obtained in every case but one — that of a boy who had been returned to the house from the infectious wards after two favorable bacteriological examinations.

A rule was now made that all new patients should be injected in the bath-room before being allowed to enter the wards for the first time, and the dose of antitoxin was increased to ten cubic centimetres for children ten years of age or over. I do not believe that the injections have been omitted or deferred a dozen times on account of the condition of any child's health, and I have seen but one instance in which danger was

suggested by the use of the serum — a case which I shall refer to later on. The mere inspection of noses and throats was soon found to be a very slight safeguard against the introduction of the bacillus, for children with apparently normal mucous membranes were frequently discovered to have bacteriological diphtheria a day or two after entering the hospital, and emergency cases were often found to be in the same plight. One of the latter developed diphtheritic membrane; and while all this went to prove the reliability of antitoxin as an immunizing agent, bitter experience had rendered us timid, and the rules for admission were amended so far as to exclude all applicants until they had been reported as free from the bacillus, excepting cases of the greatest urgency. Meanwhile, all patients found guilty of secreting (and perhaps excreting) the Klebs-Löffler were transferred to the infectious wards, there to remain until negative reports of their cultures should set them free.

No signs of the enemy were present again in any patient whose mucous membranes were free at the start, until February 15th, when a boy who had been twice immunized — the second time on January 29th — and whose cultures had always given negative results, was found to be infected. Injections were at once given in all cases which had not been immunized within two weeks, and the rule established, to repeat them every fortnight.

March 12th, a patient who through an oversight had been given no antitoxin since February 16th, was found to have the bacillus; but we had now become quite accustomed to its presence, and so long as it had not been detected in any child who had begun with a clean record, in a shorter space of time than seventeen days after immunization, we felt pretty safe so long as the injections were regularly given every two weeks.

The next day, however, a positive culture was obtained in the case of a patient who had been injected February 28th. This eclipsed any previous records, and showed that fourteen days could not be surely counted on, so the period allowed to intervene between the immunizations was shortened to thirteen days. Meanwhile an estimate of the applicants for admission whose cultures were positive, showed that over 20 per cent. had the bacillus in their throats or noses. Emergency cases came thick and fast (emergency is an elastic term from a surgical standpoint) and when the observation rooms in which such cases were kept (pending reports from the bacteriological laboratory) happened to be full, they went into the common wards. Some of these proved to have bacteriological diphtheria, and one developed clinical evidence of the disease. There is not the slightest doubt that many patients in the house were thoroughly exposed, aside from the infection present in the building itself. Our contagious wards were now full, and the question of continuing to admit patients, and allowing such patients as might present bacteriological but no clinical evidence of the disease to remain in the open wards (or even to be transfered to them from the contagious quarters) was discussed. I thought at the time, and I still think that this could have been done with safety so long as immunization was regularly kept up. There had been but few days during the past month when the wards had been free from the bacillus either alone, or as a companion to membrane. A large majority of the staff agreed with me; but we refrained from pursuing a course which might injure the hospital by giving rise to distorted rumors.

So a vote was passed to the effect that every patient with the bacillus present, whose culture had not been tested by injecting a guinea-pig, should remain in the

infectious wards, and admissions to the hospital suspended; for if measles or scarlet fever broke out among the children we should find ourselves badly crippled. Everything considered, I am sure that the staff is entitled to the credit of showing a considerable degree of deference to the somewhat freely expressed opinion of outsiders, who know but little about the actual situation. Fortunately the bacilliary tide began to ebb at this time, and we were spared the guinea-pig test, which often consumes a fortnight's time, and may lead to no really definite conclusion in the end.

Things now went along smoothly until March 25th, when an unmistakable break-down occurred in a child who had been antitoxined on the 10th, and again (by mistake) on the 16th. Negative cultures had been obtained on the 4th and 19th, but the girl had perfectly well-marked clinical diphtheria, and the diagnosis was confirmed by bacteriological examination. Within twenty-four hours bacilli, but no membrane, were found in two other cases which had been immunized on the 16th. But in spite of these exceptional cases (occurring as they did nine and ten days respectively after being injected) it was not thought best to shorten the interval between the immunizations, as I had good reasons for doubting the reliability of the serum used in these instances. April 4th, but two patients remained in the infectious wards, and as the service was becoming less active we no longer made surgical patients wait for bacteriological examinations before admitting them to the house. Two or three proved to be infected (inasmuch as the bacillus was present in their throats and such cases must be regarded as infectious no matter how robust their general health may be until their cultures have been proved benign by the guinea-pig test) and were allowed to remain in an open ward; the epidemic

was on the wane, the infectious wards were quite empty, and we did not care to reopen them. In short, we did now what we might have safely done weeks before, and for better reasons. No bad results followed this course, and I am sorry it was not pursued at an earlier date. Children who had the bacillus but no symptoms requiring special care, might far better have remained in the house and passed their time in being cured of the affections they entered the hospital for originally, than have gone to the infectious wards and increased the work of the staff and nurses. Certainly nobody who is familiar with the conduct of children in hospitals — their close intimacies, the manner in which toys are used by all — can believe that the risk of infection would have been materially increased over what already existed if they had been allowed to remain.

An analysis of all the cases, shows that of a total of 438 immunizing injections given between January 13th and May 13th, 109 were of Gibier's serum; 104 of Behring's; 74 of Aronson's; and 151 of the antitoxin prepared by the Massachusetts State Board of Health. The largest number administered to one child was seven. Many of these patients were under treatment for acute diseases at the time of injection: croupous and broncho-pneumonia, grippe, tubercular peritonitis, empyema, typhoid, or such surgical troubles as naturally find their way to a children's hospital. No special symptoms were noted as produced by the serum with regard to the existent diseases at the time of injection excepting in one or two suppurative hip cases, in which there was a temporary improvement in the appetite and general condition. In a few cases of desperate illness the antitoxin was omitted, or postponed until the patient's condition improved; but as a rule, all fared alike. I have failed to observe any dan-

gerous symptoms arise from immunization excepting one case—a boy, aged two, with leucocytosis and a large spleen, upon whom two preceding doses had produced no ill effect, had a temperature of 105.4° F. and considerable edema about the point of injection (given in the abdominal wall in this instance), and certainly appeared very sick. Cold baths and brandy soon made him better, however, much to my relief. Of course, the results of an analysis of our cases are by no means claimed to be conclusive. They are, however, sufficiently well based to permit their being regarded as suggestive. As a rule, the temperature goes up less than a degree a few hours after immunization, and in 75 per cent. of all cases this is all there is to be seen. Erythema around the point of injection occurred in 23 cases. In four it was very extensive, and closely resembled erysipelas — in one instance the child was isolated. The average duration of this symptom is three days; in some cases it lasts only a few hours. It usually appears on the first day after antitoxin, and never later than the eighth. Urticaria occurred 28 times. The frequency, severity, time of appearance, and duration of this symptom varies greatly with the brand of serum employed. That of Gibier (Pasteur Institute of New York), produced it in 22 per cent. on the (average) seventh day, and lasting (an average of) two and a half days. Behring's caused it in but one case, appearing on the eighth day and lasting three days. Aronson's gave rise to no urticaria. The serum of the Massachusetts State Board of Health produced in about four and a half per cent. an eruption, appearing on the (average) second day, and disappearing in a day and a half. This serum at present very rarely gives rise to anything cutaneous, although at first urticaria was of pretty common occurrence. In three instances the erythema was papular, and very

closely resembled measles. In two instances an eruption like scarlet fever was present. Occasionally a child whose skin remained clear after the first or second or third immunization, broke out with an erythema, or an urticaria after a subsequent injection. The same brand of serum may produce an urticaria, an erythema, or no skin eruption whatever in the same subject, as proved in more than one instance where repeated injections were given. Pain (at times intense) was noticed about the point of injection in sixteen; edema in seven; axillary or inguinal glands enlarged in three; general malaise (in one instance a mild delirium) in three. Pain in the articulations in less than one per cent. Nausea, with or without vomiting, in two per cent. Diarrhea (ephemeral) in less than three per cent. Increased frequency of micturition was noted in rare instances. The urine of 82 children was very carefully examined with reference to the effects of antitoxin on the kidneys, and the result of 540 examinations may be briefly stated as follows: In 20 per cent. no change whatever was detected. Of the remaining 80 per cent., those which had been free from albumin previous to immunization, showed a slight trace — in most instances the slightest possible amount, which could be detected only when placed in front of a dark back-ground. This within twenty-four or forty-eight hours after injection. In cases where albumin had been present before the use of antitoxin, there was a very slight increase of the amount. In no case was there any diminution in the amount passed, or any evidence of failure to eliminate properly. Repeated microscopic examinations revealed nothing more than an insignificant amount of renal irritation in any case; and when the albuminuria was produced by antitoxin, it disappeared in a period varying from two or three days to a fortnight.

With regard to the protection afforded by antitoxin, our experience has tended to show that the serum, when fresh, can be relied upon to immunize against anything resembling clinical diphtheria thirteen days, and very probably for a longer space of time. Moreover, in no instance was the bacillus detected in the nose or throat of any child who started with a clear record in a shorter space of time than that just mentioned. This last point (if eventually established) is of practical importance as showing that an immunized child is not only safe from diphtheria, but is also safe as concerns others for a definite length of time. I am by no means sure that daily examinations of cultures from every case might not have shown the fallacy of the theory; but the fact that quite numerous examinations were made, with the results described, certainly deserves mention. In the cases which broke down in eight and ten days after being immunized, the serum used had become decomposed. The color differed from that usually presented, but so slightly at the time of injection that it was used without hesitation. Forty-eight hours later it was of the color of milk.

Regarding the use of antitoxin for curative purposes, our experience, while decidedly favorable, has been too slight to warrant the expression of an opinion. Statistics at the Children's Hospital. if made up from the standpoint that the mere presence of the bacillus in the nose or throat constitutes diphtheria, would justify the extremely favorable and entirely fallacious statement, that our mortality has been less than three per cent. For of 34 patients who have been inmates of the infectious wards, only one died; and all of them received antitoxin — the great majority, however, never more than one small injection, for the purpose of immunization upon entrance, before

the reports of their cultures had been obtained. Assuredly one might as well claim, that the existence of the pneumococcus in the saliva implies the presence of pneumonia, as to call all cases which have the Klebs-Löffler bacillus, diphtheria. Equally absurd is it to treat such cases with antitoxin, unless some clinical evidence of the disease is present. I have convinced myself that full doses of the serum has no influence on the mere presence of the bacillus after it has once obtained a foothold. The more ardent supporters of the treatment, will greatly endanger its reputation if they present claims based on statistics such as I have described. On the other hand, I do not doubt that equally enthusiastic opponents of antitoxin will bring forward abundant proof that it does no good whatever. I can well remember something of the kind being done in the case of salicylic acid, and kindred preparations, by conscientious men, who showed by apparently flawless statistics, that cases of acute rheumatism did better under the old treatment by alkalies; but the remedies whose merits they denied, have stood the test of time wonderfully well, and if taken away from us to-day would be badly missed.

Results of the serum treatment, if they are to inspire confidence, must be based upon such cases as are clinically diphtheria, and the diagnosis of which is confirmed by bacteriological examination. Care must be taken to exclude all cases in which a membrane, which to all appearances is identical with that of diphtheria is present, but which is due to the work of other germs. Instances of this sort are far commoner than was formerly suspected — I have observed four (two at the hospital and two in private practice) during the past six months.

In the present state of our knowledge, the Klebs-Löffler bacillus may be said to resemble an idle but

extremely competent workman, who under certain unknown conditions may suddenly accomplish a wonderful task. He gives no warning of his intentions, and does not trouble himself to put on working clothes — at least none of a sort which can be recognized under the microscope.

Even such cultures as have every appearance of virulence may prove to be benign when tested, and when they look doubtful may promptly kill the injected guinea-pig. Every active diphtheritic germ is undoubtedly a Klebs-Löffler, but every Klebs-Löffler is by no means an active diphtheritic germ. On the contrary, it does not, as a rule, harm those who afford it shelter. Of 34 patients who have passed through our infectious wards at the Children's Hospital during the past six months, but seven have had anything resembling what used to be called diphtheria before the birth of the bacillus was announced in the journals, and two of these cases were caused by other germs. But I cannot doubt that the bacteriologists who have given us so much of inestimable value during the past few years, will before long extricate us from the dilemma caused by our uncertainty of the sanitary status of a person who has only bacteriological diphtheria. Until this knowledge is vouchsafed us, we must continue to regard such a one as a dangerously indefinite quantity; and in an institution like the Children's Hospital, this implies the absolute rejection of a large number of cases, and the disaffection of many others, who cannot be admitted until reports of their cultures have been obtained; for after such alterations shall have been effected during the coming summer as will render the building safe, and immunization is no longer a routine, no case can be permitted to enter which is open to suspicion of harboring the bacillus.

Another thing: Are we justified in admitting a

child on the strength of a single negative report? As to the reliability of these reports, there are defects in the present method of obtaining specimens for bacteriological examination (and very probably in any possible method) which render occasional errors unavoidable. I do not wish to be understood as questioning the skill and accuracy of the gentleman at the bacteriological laboratory who make the cultures. If there are no bacilli in the specimens handed in to them, we cannot reasonably expect positive reports; and I merely state an obvious fact when I say, that the wires used for obtaining specimens, may be justly compared with a hook which is lowered into a dark pool in the hope of jigging fish. If the fish are plenty, there is a strong probability of success — if scarce, the chances are fewer. And whether they are plenty or scarce, the element of luck must be taken into account. Of course, if membrane is present and the wire pushed under the outer edge, there is but little probability of failure.

To arrive at an estimate of the frequency of errors due to the uncertainty of bringing away bacilli on the wire when they are present, I have taken the bacteriological reports concerning patients in the infectious wards, from whom specimens were examined at short intervals, and called such negative reports erroneous as are immediately preceded and followed by positive cultures. Of 253 reports 26 were incorrect — a little more than 10 per cent. Under these circumstances I think two negative reports of specimens taken twenty-four hours apart should be obtained — nor can we then feel absolutely safe.

Some of the patients in the infectious wards were very slow in getting rid of their bacilli. One case was lodged and fed at the expense of the hospital for two months, for the sole reason that we failed to obtain

two negative reports in succession. He was in robust health, and a particularly noisy and troublesome boy. Finally he was discharged, much to the relief of all concerned.

Various means were tried in cases of that kind to hasten the departure of the bacillus. Good results were finally obtained by atomizing strained lemon juice into the noses and throats six times per diem. Cases which had resisted equally frequent applications of peroxide of hydrogen yielded promptly to this treatment. It is not a pleasant procedure. Children do not like it — but neither does the bacillus. At first it occasions considerable irritation about the nostrils and upper lip; but tolerance is soon established, and the end justifies the means. Since finishing this paper (May 13th) a sufficient number of injections of antitoxin have been given at the Children's Hospital to bring the total close to five hundred, and with no fresh evidence to alter the views which I have expressed. I think that the fact that we have not had a single abscess resulting from so many injections, speaks well for the careful attention to cleanliness on the part of the internes of the hospital, Messrs. Hall, Wylie and Washburn, whose good and painstaking work deserves mention.

In conclusion, I wish to express my thanks to Drs. Ernst and McCollom for the unvarying courtesy with which they have borne the severe strain upon their patience which the many hundred cultures made at my request must have caused them.